REMARKS

Claim Amendments

Claims 149, 154, 157, 164, 167, 170, 175, 178, 185, 188, 191, 196, 199, 206, 209 and 210 are canceled.

Claims 147, 158, 168, 179, 189 and 200 are amended to recite that the claimed antibody or antigen binding fragment thereof binds to "the second extracellular loop" of human CCR5. Support for this amendment is found in the specification, for example, at page 12, line 28 through page 13, line 1.

Claims 147 and 158 are also amended to recite an "isolated" antibody or antigen binding fragment thereof. Support for this amendment is found in the specification, for example, at page 14, line 25 and page 46, lines 6-7.

Claims 147, 168 and 189 are also amended to recite the specific chemokines "MIP-1α, MIP-1β, RANTES, or a combination thereof." Support for this amendment is found in the specification, for example, at page 12, lines 1-3.

Claims 158, 179 and 200 are also amended to recite "wherein said antibody or antigen binding fragment thereof additionally inhibits HIV infection." Support for this amendment is found in the specification, for example, at page 7, lines 26-27 and page 59, line 24 through page 60, line 23.

Claims 168 and 179, which are composition claims, are also amended to recite "a physiologically acceptable vehicle or carrier." Support for this amendment is found in the specification, for example, at page 47, lines 1-2.

No new matter is added.

Elections/Restrictions

Applicants acknowledge and thank the Examiner for the withdrawal of the restriction requirement. Applicants also acknowledge the Examiner's notice that "distinction of the antibodies with respect to binding specificity may require reinstatement of the restriction (species) election requirement" (Office Action, page 3, second paragraph).

Double Patenting

Claims 147-210 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-36 of U.S. Patent No. 6,528,625.

Applicants will file a Terminal Disclaimer to overcome the Examiner's obviousness-type double patenting rejection as appropriate upon notice of otherwise allowable subject matter in the present application. This will permit Applicants to assess the rejection in view of the claims as ultimately indicated to be allowable, since it is possible that the claims may change during the course of prosecution.

Priority

The Examiner asserts that Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120. Specifically, the Examiner asserts in this new matter rejection, that Claims 147-210 are "directed to a subgenus of antibodies not supported by the specification or within the noted priority documents as originally filed" (Office Action, page 4, last paragraph). The Examiner states that:

> [i]n particular, the claims are directed to a subgenus of CCR5 antibodies which binds '*human CCR5*' wherein the antibody or fragment is further capable of inhibiting binding of *chemokines* (MIP-1α, MIP-1β and RANTES) *or combination thereof*, to human CCR5 and which *inhibits one or more functions associated with binding of a chemokine to the receptor*.' Yet these limitations differ from the disclosure as directed at p. 11-12, to antibodies or antigen binding fragments that inhibit binding of a '*ligand*' and '*one or more functions mediated by CCR5 in response to the ligand*.' Moreover, specific support for the further subgenus of these antibodies that are chimeric, human, humanized, binds the second extracellular loop and inhibits HIV infections are not specifically noted. (Office Action, page 5, first full paragraph, emphasis in original).

Applicants respectfully disagree. Support for the previously filed amendment cited the specification at:

page 11, lines 18-19, which states: "In a preferred embodiment, the antibodies specifically bind **human** CCR5 receptor(s) . . . " (emphasis added);

page 12, lines 1-3, which states: "For example, in one aspect, the antibodies can inhibit (reduce or prevent) the interaction of receptor with a natural ligand, such as RANTES, MIP-1α **and/or** MIP-1β" (emphasis added); and

page 59, line 24 through page 60, line 23, which is entitled: "Inhibition of HIV-1 Infection by Anti-CCR5 mAbs".

Furthermore, there is no *in haec verba* requirement for newly added claim limitations as long as they are supported in the specification through express, implicit, or inherent disclosure (M.P.E.P. § 2136(I)(B), Original Eighth Ed., Latest Revision May 2004).

For the Examiner's convenience, below is a Table outlining examples of further support for the noted claim terms in the present application, and the parent applications to which priority is claimed. The present application is a continuation-in-part application of U.S. application Serial No. 08/893,911, filed July 11, 1997 (now issued as U.S. Patent 6,528,625), which is a continuation-in-part application of U.S. application Serial No. 08/739,507, filed October 28, 1996 (now abandoned).

	Present Application No. 09/870,932, filed May 30, 2001	**Parent Application No. 08/893,911, filed July 11, 1997 (now U.S. Patent 6,528,625)**	**Grandparent Application No. 08/739,507, filed October 28, 1996 (now abandoned)**
Claim Term	*Support at:*	*Support at:*	*Support at:*
human CCR5	page 3, lines 21-22, 25-26 page 11, lines 18-20 Claim 2 as originally filed	page 4, lines 10-12, 16-21 page 13, lines 31-33 Claim 2 as originally filed	page 3, lines 16-18 page 7, lines 22-24 Claim 2 as originally filed
chemokines (MIP-1α, MIP-1β and RANTES) or combination thereof	page 1, line 14 through page 2, line 5 page 3, lines 2-5 page 12, lines 1-3 Claims 30, 31 and 33 as originally filed	page 1, line 9 through page 2, line 14 page 14, lines 14-17 page 3, lines 17-18 page 7, lines 20-22 Claims 30, 31 and 33 as originally filed	page 1, lines 11-28 page 2, line 26 page 8, lines 6-9
inhibits one or more functions associated with binding of a chemokine to the receptor	page 3, lines 21-28 page 11, line 21 through page12, line 3 Claim 45 as originally filed	page 4, line 10-21 page 14, lines 2-24 Claim 45 as originally filed	page 3, lines 16-22 page 8, lines 3-9 Claim 5 as originally filed
human antibodies	page 14, lines 25-28	page 17, lines 29-34	
chimeric antibodies	page 15, lines 3, 4, 17	page 18, lines 5-9	page 10, lines 15-19
humanized antibodies	page 15, lines 3-6 and 18 page 16, lines 10-17	page 18, lines 5-9 page 19, lines 24-34	page 10, lines 15-19
binds the second extracellular loop	page 12, line 28 through page 13, line 1 Claim 27 as originally filed	page 15, lines 18-21 Claim 27 as originally filed	
inhibits HIV infection	page 7, line 17 through page 8, line 3 page 37, line 26 through page 38, line 1 page 59, line 24 through page 60, line 23 Claims 12, 15 and 25 as originally filed	page 9, lines 6-31 page 48, lines 1-28 Claims 12, 15 and 25 as originally filed	page 5, lines 3-28 page 27, line 31 through page 28, line 23 Claims 6, 11, 15 and 25 as originally filed

Therefore, Applicants' earliest effective filing date is at least October 28, 1996, except for claims having the limitation of either "human antibody" or wherein the antibody or antigen binding fragment thereof "binds to the second extracellular loop" of CCR5, which have a priority date of at least July 11, 1997.

Claim Objections

Claims 148, 152, 159, 162, 169, 173, 180, 183, 190, 194 and 204 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicants respectfully disagree. Claims 148, 159, 169, 180, and 190 are narrowing claims because of the recitation that the antibody has "**specificity**" for human CCR5, as opposed to an antibody that "binds human CCR5." Not all antibodies that bind to an antigen are necessarily specific for only that antigen. Claims 152, 162, 173, 183, 194 and 204 are narrowing because the claimed antibody is a "**human** antibody or an antigen binding fragment thereof" that binds human CCR5, as opposed to "an antibody or an antigen binding fragment thereof" as recited in the respective independent claims. Thus, Claims 148, 152, 159, 162, 169, 173, 180, 183, 190, 194 and 204 do further limit the parent or independent claims and thus, are in proper dependent form.

Rejection of Claims 147-210 Under 35 U.S.C. § 101

Claims 147-210 are rejected under 35 U.S.C. § 101 on the grounds that the claimed invention is directed to non-statutory subject matter. Specifically, the Examiner asserts that the "claims do not reflect isolation, or the hand of man and read on a naturally produced product of nature" (Office Action, page 6, item 9).

As noted above, Applicants have canceled Claims 149, 154, 157, 164, 167, 170, 175, 178, 185, 188, 191, 196, 199, 206, 209 and 210 and amended Claims 147 and 158 to recite an isolated antibody, as appropriate. Thus, Claims 147 and 158, and claims dependent thereon, are directed to statutory subject matter.

As amended, Claims 168 and 179, and claims dependent thereon, are directed to a composition comprising, *inter alia*, an antibody or an antigen binding fragment thereof and a

physiologically acceptable vehicle or carrier. Such compositions are not naturally produced products of nature, and thus, the claims are directed to statutory subject matter.

Claims 189 and 200, and claims dependent thereon, are directed to a test kit, comprising, *inter alia*, an antibody or an antigen binding fragment thereof and one or more ancillary reagents. Such test kits are not naturally produced products of nature, and thus, the claims are directed to statutory subject matter.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 147-210 Under 35 U.S.C. § 112, First Paragraph - Written Description

Claims 147-210 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner alleges that the specification does not reasonably convey that Applicants were in possession of the claimed invention at the time the application was filed. The Examiner asserts that this is a new matter rejection "as the claims are now directed to a subgenus which constitutes a departure from the original specification" (Office Action, page 7, bridging paragraph from page 6). In particular, the Examiner asserts that:

> the instant claims are directed to a subgenus of CCR5 antibodies which binds "*human* CCR5" wherein the antibody or fragment is further capable of inhibiting binding of *chemokines* (MIP-1α, MIP-1β and RANTES) *or combination thereof*, to human CCR5 and which *inhibits one or more functions associated with binding of a chemokine to the receptor*." Yet these limitations differ from the disclosure as directed at p. 11-12, to antibodies or antigen binding fragments that inhibit binding of a "*ligand*" and "*one or more function mediated by CCR5 in response to the ligand*." Moreover, specific support for the further subgenus of these antibodies that are chimeric, human, humanized, binds the second extracelluar [sic] loop and inhibits HIV infection are not specifically noted. (Office Action page 7-8, bridging paragraph, emphasis in original).

Applicants respectfully disagree. As noted in the Table above, each of the claim limitations "human CCR5," "chemokines (MIP-1α, MIP-1β and RANTES) or a combination thereof," "inhibits one or more functions associated with binding of a chemokine to the receptor," and antibodies that are "chimeric," "human," "humanized," "binds the second

extracellular loop" and "inhibits HIV infection" are supported by the specification and claims as filed. The claims now pending are not a departure from the specification as filed. Thus, Applicants have demonstrated possession of their claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 147-210 Under 35 U.S.C. § 112, First Paragraph - Enablement

Claims 147-210 are rejected under 35 U.S.C. § 112, first paragraph, because "the specification, while being enabling for antibodies or antigen binding fragments thereof that inhibit binding of chemokine ligands MIP-1α, MIP-1β and RANTES to human CCR5, and for the specific deposits of antibodies 5C7 and 2D7 as noted in the deposits; does not reasonably provide enablement for antibodies with such functional recitations specific to chemokine binding, functions associated with binding of a chemokine to the receptor to antibodies or to specific epitope regions such as the second extracellular loop" (Office Action page 8, item 11).

Specifically, the Examiner asserts that the claims are "drawn generically to any chemokine capable of binding human CCR5" (Office Action page 8, last sentence). Furthermore, the Examiner asserts that "the disclosure of a single species of CCR5 (human) and three chemokines bound by human CCR5 (i.e., MIP-1α, MIP-1β, and RANTES) does not appear to provide sufficient guidance to direct a person of skill in the art in how to make and use an antibody which inhibits binding of any 'chemokine' to a CCR5 protein of any mammalian origin" (Office Action, page 9, second full paragraph).

Applicants respectfully disagree for the reasons set forth in the previous Amendments. However, in an effort to advance the prosecution of the application, Applicants have amended the claims such that all of the independent claims recite antibodies or antigen binding fragments thereof that inhibit binding of chemokine ligands MIP-1α, MIP-1β and RANTES to human CCR5 to recite MIP-1α, MIP-1β, and RANTES.

The Examiner has also asserted that:

> [t]he claims as directed to inhibiting binding of any 'chemokine' to the receptor are akin to a single means claim, i.e., where a means recitation does not appear in combination with another recited element of means. Such recitations are subject to an undue breadth rejection under 35 USC 112, first paragraph because the

> specification at most would only disclose those means known to the inventor at the time of the invention, see in particular MPEP 2164.08(a). Here no other chemokines capable of such binding are known or disclosed other than MIP-1α, MIP-1β and RANTES (Office Action page 9-10, bridging paragraph).

Applicants are unclear about the basis for this rejection. A single means claim applies when claims depend on a recited *property* where the claim covers *every conceivable structure* (means) for achieving the stated property (result) (see M.P.E.P. § 2164.08(a), Original Eighth Ed., Latest Revision May 2004). Applicants point out that the claims do not only depend on a recited property wherein every conceivable structure is claimed. The claims are directed to, *inter alia*, an antibody or antigen binding fragment thereof that inhibits binding of a chemokine to human CCR5. Applicants are not claiming every conceivable structure (only an antibody or antigen binding fragment thereof) to achieve the stated property (*inter alia*, inhibiting binding of a chemokine to human CCR5). Still further, Applicants believe the amendment to the claims to recite MIP-1α, MIP-1β and RANTES, renders the rejection is moot in view of the Examiner's comments regarding MIP-1α, MIP-1β and RANTES being those chemokines which are known and disclosed by Applicants. In the event the Examiner maintains the rejection on the basis of a single means claim, Applicants respectfully request clarification.

The Examiner also asserts in this rejection that, with respect to:

> the new recitations directed to 'inhibit(ing) HIV infection,' the specification teaches that specific monoclonal antibodies with epitope specificity within the region of the amino terminus or second extracellular loop were capable of inhibiting binding and entry of HIV. . . . In contrast, only antibodies with epitopes specific to the second extracellular loop were capable of inhibiting binding of chemokines MIP-1α, MIP-1β and RANTES to human CCR5. (Office Action page 10, first full paragraph).

Thus, the Examiner concludes that "the claims do not delineate these apparent structural constraints of the antibody variable domains. Further the claims fail to recite the epitope specificity apparently required for conveying these properties, i.e., specificity for the second extracellular loop" (Office Action page 11, first full paragraph).

Applicants respectfully disagree for the reasons already of record. However, in view of Applicants' amendment to the independent claims to recite binding of the claimed antibody or antigen binding fragment thereof to the second extracellular loop of human CCR5, the rejection is moot.

The Examiner also asserts that "as to claim 185, a composition is recited, yet only an antibody or antigen binding fragment is provided. The composition is absent any other element. Thus, the claim does not direct suitable for a composition and therefore is non-enabling as to the preamble recitation" (Office Action page 11, second full paragraph).

Applicants are unclear about the basis for the rejection. Applicants respectfully traverse this rejection and submit that a composition claim does not necessitate the recitation of more than one element. In an effort to expedite prosecution of the application, Applicants have amended the independent composition claims (Claims 168 and 179) to additionally recite a physiologically acceptable vehicle or carrier. If the Examiner is asserting that a composition claim must recite more than one component in order to be a composition, then this amendment renders the rejection moot. Dependent Claim 185 has been canceled.

Additionally, the Examiner notes that "Applicant's arguments in traverse of the art rejections of record support the aforementioned scope of enablement rejection. . . . To the extent that applicants argue the prior art as non-enabling, so to does Olson support non-enablement within the full scope of the claims absent specific guidance as to those structural and functional characteristics of a genus of antibodies capable of providing the recited functions" (Office Action pages 11-12, bridging paragraph).

Applicants respectfully disagree. However, as noted above, Applicants have amended the claims to recite binding of the claimed antibody or antigen binding fragment thereof to the second extracellular loop of human CCR5, therefore, the rejection is moot.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 147-210 Under 35 U.S.C. § 112, First Paragraph - Written Description

Claims 147-210 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner states that "[a]bsent a sufficient description of the receptor-ligand pairs, or a means for immediately recognizing those chemokines that readily bind, there is not adequate written description support of the genus as directed to antibodies or antigen binding fragments that inhibit binding of any chemokine to the human CCR5 receptor and further that provides for inhibition of one or more ill described functions associated with binding of the chemokines to the receptor" (Office Action page 14, paragraph continued from page 13). Furthermore, the Examiner states that "the specification teaches the apparent requirement for the antibody or antigen binding fragment to be specific to the second extracellular loop in order for the antibodies to provide the noted functional characteristics, yet such is not an element of the claims, nor is there sufficient support to denote that this division is a further sub-species or sub-genus readily contemplated by Applicnats [sic]" (Office Action page 14, first full paragraph). The Examiner further asserts that, with respect to claims directed to inhibiting HIV infection, "only antibodies to the second extracellular loop of CCR5 were capable of inhibiting binding of chemokines MIP-1α, MIP-1β and RANTES to human CCR5 and inhibiting HIV binding and entry. These specifics are not limitations of the claims" (Office Action, page 14-15, bridging paragraph). The Examiner notes that "[t]o the extent that applicants argue the prior art as not-sufficiently [sic] described (for lacking particular description of the properties), so to is Applicant's specification lacking in the description of those structural characteristics providing the recited functional constraints" (Office Action pages 15-16, bridging sentence).

Applicants respectfully disagree for the reasons set forth in the previous amendment. However, as noted above, Applicants have amended the claims to recite the chemokines MIP-1α, MIP-1β and RANTES and to recite that the antibody or antigen binding fragment thereof binds to the second extracellular loop of human CCR5. It is also noted that Applicants have clearly considered binding of the second extracellular loop as a limitation since this limitation was presented, for example, in Claim 27 as originally filed and previously filed dependent Claims 154, 164, 175, 185, 196 and 206 (now canceled in view of the current claim amendments). Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 147-210 Under 35 U.S.C. § 102(b) and 102(e)

Claims 147-210 are rejected under 35 U.S.C. § 102(b) and 102(e) as being anticipated by Li *et al.*, (U.S. Patent No. 6,025,154; IDS Ref. AE) as evidenced by Wu *et al.*, (J. Exp. Med. 1997; 186(8):1373-1381; IDS Ref. AS4) Samson *et al.*, (J. Biol. Chem., 1997: 272: 24934-41), Raport *et al.*, (*J. Biol. Chem. 271*:17161-17166 (1996); IDS Ref. AW) Combadiere *et al.*, (*J. Leukoc. Biol. 60*:147-152 (1996); IDS Ref. AT3) and Atchison (Science, 274:1924-1926 (1996); IDS Ref. AZ5). Specifically, the Examiner asserts that the "selection of chemokines MIP-1α, MIP-1β and RANTES that bind CCR5 is not an inventive contribution as suggested by applicants. Such ligands were *already recognized* as ligands binding CCR5 and mediating receptor signaling" (Office Action page 17, second paragraph, emphasis added) citing Raport *et al.* and Combadiere *et al.* in support thereof. The Examiner concludes that "the Li reference does teach and is enabling for the screening of the *specifically known ligands* as well as their receptor functions as established in the art" (Office Action page 17-18, bridging sentence; emphasis added).

Applicants respectfully disagree.

Li *et al.* is not prior art under 35 U.S.C. § 102(b)

As a preliminary matter, Applicants note that the rejection is not properly applied under 35 U.S.C. § 102(b) which applies when "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States" (35 U.S.C. § 102(b)). Li *et al.* issued on February 15, 2000, which is not more than one year prior to Applicants' effective filing date, and, indeed, is after Applicants' effective filing date.

Li *et al.* cannot be an anticipatory reference because it does not enable the claimed invention

The courts have consistently held that "[t]o serve as an anticipating reference, the reference must enable that which it is asserted to anticipate" *Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education and Research*, 346 F.3d 1051, 1054, 68 U.S.P.Q.2d 1373, 1375 (Fed. Cir. 2003); "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled" *Amgen, Inc. v. Hoechst*

Roussel, Inc., 314 F.3d 1313, 1354, 65 U.S.P.Q.2d 1385, 1416 (Fed. Cir. 2003). See also M.P.E.P. § 2121.01, Original Eighth Ed., Latest Revision May 2004). In deciding whether or not a disclosure is enabled, the pertinent question is whether the experimentation needed to practice the invention is undue or unreasonable. The factors to be considered include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988)

Li *et al.* does not disclose *any* chemokine as a CCR5 ligand. Nor does Li *et al.* disclose *any ligand* of CCR5. Li *et al.* was filed on June 6, 1995. Raport *et al.* and Combadiere *et al.* were both published in July 1996, *more than one year after* the filing date of Li *et al.* Therefore, the Examiner has not evidenced that *any* ligands of CCR5 were *known* at the time of Li *et al.* The state of the art at the time of Li *et al.* was such that *no specific ligands of the receptor disclosed by Li et al. were known by Li et al. or by others.* Thus, Li *et al.* provides no guidance as to which ligand or chemokine would bind to CCR5.

Furthermore, Li *et al.* does not disclose any working examples of assays used to produce or identify an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human (CCR5), wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor.

Considering the *Wands* factors, Li *et al.* is not an enabling reference because it would require extensive experimentation for one of skill in the art to use the assay described by Li *et al.* due to the failure to disclose any CCR5 ligands. Without disclosure of any CCR5 ligands by Li *et al.*, there is a lack of any guidance to perform the assay. Furthermore, Li *et al.* lacks of any working examples. The relative skill of those in the art (who did not know of any ligands, including chemokines, that bind to CCR5), means that the Li *et al.* assays which require the use of a receptor ligand to identify potential antibodies that bind to the receptor, cannot be performed by one of ordinary skill in the art based on the teachings of Li *et al.* As stated in *Elan*, 346 F.3d

at 1055,"[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation."

Thus, Li *et al.* is not an enabling reference for an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human (CCR5), wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor because it would require undue experimentation for a person of ordinary skill in the art. Without an enabling teaching of each and every aspect of Applicants' claimed invention, Li *et al.* is not anticipatory under 35 U.S.C. § 102.

Li *et al.* does not inherently disclose the claimed invention because the antibodies do not necessarily and inherently include all elements of the claimed invention

For anticipation under 35 U.S.C. § 102, the reference *must teach* every aspect of the claimed invention *either explicitly or impliedly*. Any feature not directly taught must be *inherently* present (M.P.E.P. § 706.02(IV), Original Eighth Ed., Latest Revision May 2004; emphasis added). For a reference to anticipate by inherency, it is required that "the prior art *necessarily* functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (emphasis added). Furthermore, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (emphasis in original; citations omitted).

Contrary to the Examiner's assertion, the screening assay of Li *et al.* would *not necessarily* result in the identification of an antibody or antigen binding fragment thereof specific to the second extracellular loop of CCR5. Li *et al.* merely provides a generic statement that antibodies, including antagonists, to CCR5 can be made. This disclosure by Li *et al.* does not allow one of ordinary skill in the art to "at once envisage" an isolated antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor. No

chemokines were known or disclosed by Li *et al.* to bind to CCR5, and thus, one of skill in the art could not anticipate any antibody as claimed by Applicants.

Furthermore, even if one of skill in the art could use an assay as described by Li *et al.* to screen for an antibody or antigen binding fragment that binds CCR5, it would not be *necessary and inevitable* that any particular antibody or antigen binding fragment thereof would bind to the second extracellular loop of a human CCR5, inhibit binding of MIP-1α, MIP-1β or RANTES, and inhibit one or more functions associated with binding of the chemokine to the receptor. As indicated in the Declaration of Walter Newman, Ph.D. under 37 C.F.R. § 1.132 (the "Declaration"), previously submitted in parent application no. 08/739,507 as Exhibit A and again submitted with the Amendment filed on April 11, 2003, in the pending application, not all antibodies which bind to CCR5 necessarily have the ability to inhibit binding of a ligand to a receptor (Declaration, paragraph 5). See also Olson *et al.*, "[c]hemokine receptor-binding agents can be antagonists or, more rarely, agonists of receptor-mediated intracellular signaling. Alternatively, they could have no effect on signaling" (page 4147, column 2, last paragraph).

Thus, because the assay described by Li *et al.* to screen for an antibody or antigen binding fragment that binds CCR5 would not *necessarily and inevitably* identify an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor, the disclosure of Li *et al.* does not anticipate the claimed invention.

The Examiner has cited Wu *et al.* and Samson *et al.*, as secondary references to support the assertion that "the Li chemokine binding region is within the second extracellular loop" (Office Action page 18, first paragraph).

The Examiner has cited these references apparently to show that characteristics not disclosed by Li *et al.* are inherent. However, such a showing requires that the secondary reference "must make clear that the missing descriptive matter is *necessarily present* in the thing described in the reference, and that it would be so recognized by persons of ordinary skill" (MPEP, 8th edition, Latest Revision May 2004, § 2131.01 III, emphasis added; citing *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991)).

Wu *et al.* describe "a number of mAbs that inhibit the various interactions of CCR5" (Summary), *one* of which was an antagonist of CCR5. Notably, Wu *et al.* describe that "[a] preliminary analysis of a panel of anti-CCR5 mAbs revealed that *none* of the eight previously identified anti-CCR5 mAbs was able to block the binding of CCR5 ligands RANTES, MIP-1α, or MIP-1β to CCR5" (page 1375, second column, first full paragraph; emphasis added). Clearly, any particular anti-CCR5 antibody does not *necessarily* include an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor.

Samson *et al.* describe that the "region of CCR5 involved in its specific interaction with MIP-1α, MIP-1β and RANTES, and its subsequent activation, lies within the second extracellular loop (*and possibly the adjacent transmembrane segments*)" (Abstract; emphasis added). Samson *et al.* also note that "[r]elatively little is known concerning the structure-function relationships of CC-chemokine receptors and their ligands, in general" (page 24934, column 2, first full paragraph). Importantly, Samson *et al.* also caution "[i]t should be stressed that chimeric receptor-based studies, such as ours, can only discriminate domains important for ligand selectivity. Conserved regions that would be required for ligand binding and/or functional response to the ligands could easily be overlooked" (page 24940, first column, third full paragraph). Thus, this secondary reference does not make clear that the missing descriptive matter in Li *et al.* is *necessarily present* in the assay described by Li *et al.*, and that it would be so recognized by persons of ordinary skill.

The Examiner has also cited Samson *et al.*, and Atchison as secondary references to support the assertion that "this site [the second extracellular loop] is also evidenced as the major co-receptor allowing infection of HIV. . . . Hence, the screening assay of Li would further necessarily identify antibodies capable of inhibiting infection of HIV as the ligand binding site of the second extracellular loop is critical to HIV infection" (Office Action page 18, first paragraph).

Again, the Examiner has cited these references apparently to show that characteristics of the claimed antibodies not disclosed by Li *et al.* are inherent. However, as already noted, such a showing requires that the secondary reference "must make clear that the missing descriptive

matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill" (MPEP, 8th edition, Latest Revision May 2004, § 2131.01 III, emphasis added; citing *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991)).

Samson *et al.* describe that the "NH_2 terminus and the *first extracellular loop of CCR5* are responsible for the specificity of interaction with M-tropic HIV-1 strains" (page 24934, column 2, first full paragraph; emphasis added). In fact, they emphasize that "it is clear that the regions of CCR5 involved in chemokine ligand specificity, and in the specificity of cofactor usage for various HIV-1 strains are not identical" (page 24940, column 1-2, bridging sentence). Thus, Samson *et al.* clearly fails to demonstrate that the missing descriptive matter of Li *et al.* is *necessarily* present in the assay described in Li *et al.*, and that it would be so recognized by persons of ordinary skill.

Atchison describe "elements within both the NH_2-terminus and distal portions of the receptor are contributory to HIV-1 coreceptor activity, whereas neither element alone is essential" (page 1924, column 3, first paragraph). Thus, like Samson *et al.*, Atchison fails to demonstrate that the missing descriptive matter of Li *et al.* is *necessarily* present in the assay described in Li *et al.*, and that it would be so recognized by persons of ordinary skill.

The Examiner also noted that "Olson unlike Li, did not select for antagonists (antibodies) inhibiting chemokine binding but rather antibodies that blocked HIV mediated fusion. . . . Such identified antibodies were subsequently tested for their effect on chemokine binding. Thus, Olson is directed to a different screen and does not teach away from the screening taught by Li" (Office Action, page 17, second paragraph). In the previous Amendment, Applicants cited Olson *et al.* to illustrate that antibodies which bind CCR5 may not inhibit of a chemokine and/or inhibit one or more functions associated with binding of a chemokine to the receptor. Olson *et al.*, which is discussed in further detail below, screened 10,000 hybridoma supernatants for inhibition of HIV fusion, only six of which bound to CCR5, and none of which were tested for their ability to *block chemokine binding*. Olson *et al.* do describe testing of the six antibodies for inhibition of chemokine *signaling* (see, for example, page 4147, column 2, last paragraph), and map the epitope specificity of the six antibodies, however, only one antibody partially blocked RANTES

signaling and had an epitope specificity for both the N-terminus and the second extracellular loop of CCR5 (page 4147, column 2 to page 4148, column 1, and Table 1).

Moreover, the Examiner states that the claims reciting the deposit "absent identifying characteristics that would teach over the prior art" (Office Action, page 18, first paragraph) are rejected to the extent that the parent claims are rejected. For the same reasons discussed above, such an antibody would not necessarily and inevitably be isolated by the screen of Li *et al.*

In sum, the disclosure of Li *et al.* does not provide an enabling disclosure to effectively identify an antibody or antigen binding fragment thereof of the presently claimed invention, nor does the disclosure of Li *et al.* provide an antibody or antigen binding fragment thereof necessarily having each and every element of the claimed invention. As such, Li *et al.* is not an anticipatory reference. Therefore, in view of the discussion presented above, Applicants respectfully submit that the Examiner's rejection is not supported by the evidence as the cited art is not sufficient to anticipate the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 147-210 Under 35 U.S.C. § 102(b) and 102(e)

Claims 147-210 are rejected under 35 U.S.C. § 102(b) and 102(e) as being anticipated by Hoxie (U.S. Patent No. 5,994,515; IDS Ref. AB) as evidenced by Olson *et al.* (*J. Virol.* 1999; 73:4145-4155; IDS Ref. AW5) and Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4).

Applicants respectfully disagree. As a preliminary matter, Applicants note that the rejection is not properly applied under 35 U.S.C. § 102(b) which applies when "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States" (35 U.S.C. § 102(b)). Hoxie issued on November 30, 1999, which is not more than one year prior to Applicants' effective filing date, and, indeed, is after Applicants' effective filing date.

With respect to the rejection of Claims 147-210 under 35 U.S.C. § 102(e), the Examiner asserts that:

> Hoxie's method includes screening for antibodies capable of inhibiting HIV infection. Olson notes the most effective antibodies

> identified via such selection criteria are those that bind at the second extracellular loop, within the chemokine ligand binding domain and which inhibit calcium flux (receptor function). Thus, while it is true that other antibodies may be identified using the inhibition of envelope fusion and entry as selection criteria. Nevertheless, *Olson evidences that the claimed antibodies are* ***necessarily*** *provided using such screening techniques* as the antibodies were subsequently identified as antibodies capable of inhibiting HIV infection, inhibiting chemokine binding and receptor function. In particular, the antibodies that are the most effective at inhibiting HIV infection and *are necessarily selected* based upon this selection criteria, are noted to be specific to the ligand binding site and to inhibit calcium influx (receptor function). (Office Action pages 19-20, bridging paragraph, emphasis added).

Applicants respectfully disagree. For anticipation under 35 U.S.C. § 102, the reference *must teach* every aspect of the claimed invention *either explicitly or impliedly*. Any feature not directly taught must be *inherently* present (M.P.E.P. § 706.02(IV), Original Eighth Ed., Latest Revision May 2004; emphasis added). For a reference to anticipate by inherency, it is required that "the prior art *necessarily* functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (emphasis added). Furthermore, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co.USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (emphasis in original; citations omitted). Hoxie does not explicitly or impliedly teach or suggest every aspect of the invention. Furthermore, the missing features of Hoxie are not inherently present.

Hoxie teaches an "antiviral antibody" produced by inoculating mice with CP-MAC-infected Sup-T1 cells, and hybridomas were screened for the ability to inhibit CP-MAC-induced syncytium induction (Hoxie, column 21, lines 20-27). Of the eight monoclonal antibodies produced by Hoxie, seven reacted specifically with a viral envelope proteins (not a cellular protein) and one antibody, MAb 12G5, reacted with a cellular protein, CXCR4 (Hoxie, column 7, lines 33-37 and lines 49-50). MAb 12G5 did not recognize CCR5 (column 25, lines 18-20). Hoxie generically teaches that an antibody can be raised against the entire CXCR4 molecule or peptides thereof (Hoxie, column 8, lines 30-39). Hoxie also suggests an antibody that binds to

CCR5 (Hoxie, column 3, lines 13-16). However, there is no teaching or suggestion by Hoxie of an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β, RANTES, or a combination thereof, and inhibits one or more functions associated with binding of the chemokine to the receptor.

Thus, since Hoxie does not teach every aspect of the claimed invention either explicitly or impliedly, the missing aspects of the antibody or antigen binding fragment thereof binding to the second extracellular loop of CCR5, inhibiting binding of a chemokine such as MIP-1α, MIP-1β, RANTES, or a combination thereof, and inhibiting one or more functions associated with binding of the chemokine to the receptor must be inherently present in Hoxie for it to qualify as an anticipatory reference.

Olson *et al.* and Wu *et al.* were cited by the Examiner as secondary references, presumably to evidence that the missing aspects of the invention in Hoxie are inherently present.

Applicants respectfully disagree that Olson *et al.* and Wu *et al.* evidence that the missing aspects of the invention in Hoxie are inherently present in Hoxie. Applicants note that Olson *et al.* (May 1999) describe a similar assay as Hoxie to produce monoclonal antibodies, but in this case to bind CCR5. Olson *et al.* report that "[o]f *10,000 hybridoma supernatants* screened, well over 100 inhibited fusion by >50%, but *only 6* – designated PA8, PA9, PA10, PA11, PA12, and PA14 – specifically and intensely stained L1.2-CCR5$^+$ but not the parental L1.2 cells" (page 4147, column 1, first paragraph; emphasis added). Five of the six MAbs (PA8, PA9, PA10, PA11 and PA12) from the 10,000 hybridoma supernatants were *unable to inhibit Ca^{2+} influxes induced by RANTES* (page 4147, column 2, last paragraph).

Thus, contrary to the Examiner's assertion, Olson *et al.* do *not* evidence that Applicants' claimed subject matter is *necessarily* provided using the screening techniques of either Hoxie or Olson *et al.*, i.e., isolating an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor. Therefore, the absent aspects of the claimed invention are not evidenced by Olson *et al.* to be inherent in Hoxie. As already noted, inherency "*may not be established by probabilities or possibilities. The mere fact that a certain thing may*

result from a given set of circumstances is not sufficient." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (emphasis added; citations omitted).

Wu *et al.* (October 1997) also fail to evidence that the absent aspects of the claimed invention in Hoxie are inherent. Nothing in Wu *et al.* establishes that Hoxie would necessarily provide an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β, RANTES, or a combination thereof, and inhibits one or more functions associated with binding of the chemokine to the receptor. The teachings of Wu *et al.*, which characterize the antibody 2D7, cannot show that the absent aspects of the claimed invention in Hoxie are inherent.

The Examiner has also stated that the claims reciting the deposit "absent identifying characteristics that would teach over the prior art" (Office Action, page 20, first paragraph) are rejected to the extent that the parent claims are rejected. For the reasons discussed above, such an antibody would not necessarily and inevitably be identified by the screen of Hoxie.

Thus, because Hoxie does not teach every aspect of the claimed invention either explicitly or impliedly, Hoxie does not anticipate the invention of Claims 147-210. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 147-210 Under 35 U.S.C. § 102(b) and 102(e)

Claims 147-210 are rejected under 35 U.S.C. § 102(b) and 102(e) as being anticipated by Littman *et al.* (U.S. Patent No. 5,939,320; IDS Ref. AA) as evidenced by Olson *et al.* (*J. Virol.* 1999; 73:4145-4155, IDS Ref. AW5) and Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4).

Applicants respectfully disagree. As a preliminary matter, Applicants note that the rejection is not properly applied under 35 U.S.C. § 102(b) which applies when "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States" (35 U.S.C. § 102(b)). Littman *et al.* issued on August 17, 1999, which is not more than one year prior to Applicants' effective filing date, and indeed is after Applicants' effective filing date.

With respect to the rejection of Claims 147-210 under 35 U.S.C. § 102(e), the Examiner asserts that:

> Littman's method is for screening for antibodies capable of inhibiting HIV infection. Olson notes the most effective antibodies identified via such selection are those that bind at the second extracellular loop, within the chemokine ligand binding domain and which inhibit calcium flux (receptor function). Thus, while it is true that other antibodies may have been identified using such selection criteria, nevertheless, *Olson evidences that the claimed antibodies are* ***necessarily*** *provided.* In particular, these are the antibodies that are the most effective at inhibiting HIV infection and would *necessarily be selected and identified* based upon the noted selection criteria. (Office Action page 21, first paragraph, emphasis added).

Applicants respectfully disagree. As already stated, for anticipation under 35 U.S.C. § 102, the reference *must teach* every aspect of the claimed invention *either explicitly or impliedly.* Any feature not directly taught must be *inherently* present (M.P.E.P. § 706.02(IV), Original Eighth Ed., Latest Revision May 2004; emphasis added). For a reference to anticipate by inherency, it is required that "the prior art *necessarily* functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (emphasis added). Furthermore, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co.USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (emphasis in original; citations omitted). Littman *et al.* does not explicitly or impliedly teach or suggest every aspect of the invention. Furthermore, the missing features of Littman *et al.* are not inherently present.

Littman *et al.* generically disclose that antibodies that recognize an HIV translocation promoting protein can be generated (column 20, lines 19-26). One such HIV translocation promoting protein is CCR5. Littman *et al.* do not explicitly or impliedly teach or suggest an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β, RANTES, or a combination thereof, and inhibits one or more functions associated with binding of the chemokine to the receptor. At most, Littman *et al.* suggest that antibodies can be

generated that "agonize or antagonize the activity of [a] translocation promoting protein" (column 23, lines 1-3). Thus, since Littman *et al.* does not teach every aspect of the claimed invention either explicitly or impliedly, the missing aspects of the antibody or antigen binding fragment thereof binding to the second extracellular loop of CCR5, inhibiting binding of a chemokine such as MIP-1α, MIP-1β, RANTES, or a combination thereof, and inhibiting one or more functions associated with binding of the chemokine to the receptor must be inherently present in Littman *et al.* for it to qualify as an anticipatory reference. Again, Olson *et al.* and Wu *et al.* were cited by the Examiner as secondary references presumably to evidence that the missing aspects of the invention in Littman *et al.* are inherently present.

Applicants respectfully disagree that Olson *et al.* and Wu *et al.* evidence that the missing aspects of the invention in Littman *et al.* are inherently present in Littman *et al.* As discussed above, Olson *et al.* report that "[o]f *10,000 hybridoma supernatants* screened, well over 100 inhibited fusion by >50%, but *only 6* – designated PA8, PA9, PA10, PA11, PA12, and PA14 – specifically and intensely stained L1.2-CCR5$^+$ but not the parental L1.2 cells" (page 4147, column 1, first paragraph; emphasis added). Five of the six MAbs (PA8, PA9, PA10, PA11 and PA12) from the 10,000 hybridoma supernatants were *unable to inhibit Ca^{2+} influxes induced by RANTES* (page 4147, column 2, last paragraph). The remaining MAb (PA14) was compared with the commercially purchased MAb 2D7. Olson *et al.* disclose that PA14 required *eight times* the amount of antibody to inhibit RANTES-induced calcium mobilization as compared with MAb 2D7 (pages 4147-4148, bridging paragraph). Furthermore, the epitope specificity of PA14 is disclosed by Olson *et al.* to include *both the N-terminus and the second extracellular loop*, whereas MAb 2D7 binds exclusively to the second extracellular loop (page 4149, Table 1).

Thus, contrary to the Examiner's assertion, Olson *et al.* do *not* evidence that Applicants' claimed subject matter is *necessarily* provided in Littman *et al.*, i.e., an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor would not be isolated each time one practiced the method taught by Littman *et al.* Therefore, the absent aspects of the claimed invention are not evidenced by Olson *et al.* to be inherent in Littman *et al.* As already noted, inherency "*may not be established by probabilities*

or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co.USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991) (emphasis added; citations omitted).

Wu *et al.* (October 1997) also fail to evidence that the absent aspects of the claimed invention in Littman *et al.* are inherent. Nothing in Wu *et al.* establishes that Littman *et al.* would necessarily provide an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β, RANTES, or a combination thereof, and inhibits one or more functions associated with binding of the chemokine to the receptor. The teachings of Wu *et al.*, which characterize the antibody 2D7, cannot show that the absent aspects of the claimed invention in Littman *et al.* are inherent.

The Examiner has also stated that the claims reciting the deposit "absent identifying characteristics that would teach over the prior art" (Office Action, page 21, first paragraph) are rejected to the extent that the parent claims are rejected. For the reasons discussed above, such an antibody would not necessarily and inevitably be identified by the screen of Littman *et al.*

Thus, because Littman *et al.* does not teach every aspect of the claimed invention either explicitly or impliedly, Littman *et al.* does not anticipate the invention of Claims 147-210. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 147-210 Under 35 U.S.C. § 103(a)

Claims 147-210 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chuntharapai *et al.* (U.S. Patent No. 5,543,503; IDS Ref. AD) in view of either Raport *et al.* (*J. Biol. Chem. 271*:17161-17166 (1996); IDS Ref. AW), Samson *et al.* (*Biochem. 35*:3362-3367 (1996); IDS Ref. AV), or Combadiere *et al.* (*J. Leukoc. Biol. 60*:147-152 (1996); IDS Ref. AT3), as evidenced by Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4).

Specifically, the Examiner states that Chuntharapai *et al.*:

> notes the suggestion of making antibodies specific for a chemokine family receptor such that the antibodies bind and inhibit receptor function. The human CCR5 receptor and chemokine ligands were known in the art as well as suitable assays for assessing binding and receptor function. The suggestion and means for screening are suitably provided and the making of such antibodies, while

> requiring extensive experimentation does not involve experimentation that is undue or not well established in the art. Thus, both [sic] a reasonable expectation of success are provided. (Office Action, page 22, second full paragraph).

Applicants respectfully disagree. *In re Vaeck* sets forth a two-prong standard for establishing combined reference obviousness; both prongs of the test must be met in order for such a rejection to be proper. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Where the claimed invention is rejected as obvious in view of a combination of references, 35 U.S.C. § 103 requires both (1) that "the prior art would have suggested to those of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Additionally, the cited references must teach or suggest all of the claim limitations. "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* None of the combinations based on the cited references teaches or suggests the claimed invention which is directed to an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human (CCR5), wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor. Moreover, no reasonable expectation of success founded in the prior art exists with respect to the claimed antibodies as discussed in detail below.

Chuntharapai *et al.* suggest the production of antibodies to IL-8 receptors of the platelet factor 4 superfamily (PF4A), a family including "*several hundred* different receptors" (column 1, lines 11-14 and lines 44-47; emphasis added). Specifically, Chuntharapai *et al.* teach the production of anti-IL-8 receptor antibodies which inhibit binding of IL-8 to IL-8R. The teachings of Chuntharapai *et al.* are limited to the disclosure of an anti-IL-8R antibody which inhibits binding of IL-8 to IL-8R. Chuntharapai *et al.* do not teach or suggest that their anti-IL-8R antibody inhibits any function associated with binding of IL-8 to IL-8R. In fact, Chuntharapai *et al.* demonstrate only a binding assay because there was no good bioassay specific for IL-8R. Thus, it appears that the authors were able to test their anti-IL-8R antibody only for the ability to inhibit binding of IL-8 to IL-8R, and did not test for the ability to inhibit function associated with binding of IL-8 to IL-8R. Chuntharapai *et al.* clearly contains no teaching or suggestion to make

an antibody that binds CCR5, far less an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor.

Raport *et al.* describe the identification and characterization of cDNA encoding CCR5 and disclose that the encoded receptor binds RANTES, MIP-1α and MIP-1β. Raport *et al.* do not teach or suggest an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor.

Samson *et al.* teach the cloning of a human gene encoding chemokine receptor CCR5 and assessing of the physiological responses to various chemokines mediated by CCR5. Samson *et al.* also note that "[r]elatively little is known concerning the structure-function relationships of CC-chemokine receptors and their ligands, in general" (page 24934, column 2, first full paragraph). In particular, the reference does not disclose an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor.

Combadiere *et al.* teach the cloning of a CCR5 variant whose amino acid sequence differs from the amino acid sequence of CCR5 disclosed by Samson *et al.* at amino acid 90. Once again, Combadiere *et al.* do not teach or suggest an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor.

Applicants respectfully submit that the combination of Chuntharapai *et al.* with Raport *et al.*, Samson *et al.* and Combadiere *et al.* does not teach or suggest all of the limitations of the instant claims as required for a proper rejection under 35 U.S.C. § 103 because even the combination of references does not teach or suggest an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or

more functions associated with binding of the chemokine to the receptor. None of the cited references teaches or suggests an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor.

Chuntharapai *et al.* merely disclose an anti-IL-8R antibody which inhibits binding of IL-8 to IL-8R but do not disclose the functional effect of this inhibition. The determination that an antibody is able to inhibit binding of IL-8 to IL-8R does not mean that antibody is able to inhibit one or more functions associated with binding of the chemokine (e.g., IL-8) to receptor (e.g., IL-8R). As disclosed in Olson *et al.* and in the Declaration, an antibody which inhibits binding of a chemokine may themselves trigger receptor function by virtue of their binding to the receptor (Olson *et al.*, page 4147, column 2, lines 46-48; Declaration, paragraph 6). In this instance, inhibition of binding of the chemokine to the receptor would not inhibit the biological activities of the receptor which result from binding of the chemokine, as some or all of these activities can be potentiated by the antibody itself. The fact that an antibody which is capable of inhibiting binding of a chemokine to receptor can have several effects on the functions associated with binding of chemokine to receptor is evidenced by Frade *et al.* (*J. Immunol. 159*(11):5576-5584 (1997); IDS Ref. AY5). Frade *et al.* disclose the production of a panel of monoclonal antibodies capable of binding CCR2 as demonstrated by the fact that all six mAbs recognize THP-1 and Mono Mac 1 cells, as well as CCR2-transfected 293 cells, in flow cytometry analysis. However, an assessment of the functional effects of binding of these antibodies to the CCR2 receptor showed a widely varied functional response. Some antibodies had no effect on function in chemotaxis and calcium flux assays. Other antibodies (antagonists) inhibited one or the other of the assessed functions, while a third group of antibodies (agonists) caused an increase from baseline in one or more of the assessed functions. Thus, it is highly unpredictable from the mere disclosure of antibodies which inhibit the binding of chemokine (e.g., IL-8) to receptor (e.g., IL-8R) what the effect, if any, of such an antibody will be on functions associated with binding of the chemokine to receptor. Chuntharapai *et al.* cannot be fairly summarized as teaching an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α,

MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor, and the secondary references do not remedy this defect.

Thus, Applicants respectfully submit that the Examiner has not established a *prima facie* showing of obviousness under 35 U.S.C. § 103 because all of the claim limitations are not taught or suggested by the cited art.

Even assuming *arguendo* that the references were properly combined, whether or not the antibodies described by Chuntharapai *et al.* are capable of inhibiting chemokine binding to the IL-8 receptor, the teachings of the cited references do not establish a reasonable expectation of success in obtaining the anti-CCR5 antibodies with the requisite activity for a number of reasons.

First, CCR5 is distinct from IL-8 receptor. The prior art does *not* teach that CCR5 is equivalent to IL-8 receptor and in fact, CCR5 is *not* equivalent to the IL-8RA and IL-8RB receptors. Thus, there would be no reasonable expectation of success in making an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor founded upon the teachings related to anti-IL-8RA/RB antibodies as disclosed by Chuntharapai *et al.*, since the prior art does not teach that CCR5 is equivalent to IL-8RA or IL-8RB, and because IL-8RA/RB and CCR5 are not in fact equivalents. CCR5 has a distinct primary amino acid sequence and a different structure and function from IL-8RA and IL-8RB. For example, studies with IL-8 receptors and antibodies thereto would have no bearing on the question of whether CCR5 chemokine binding regions might be immunogenic, and thus there would be no reasonable expectation of success in obtaining an anti-CCR5 antibody which inhibits chemokine binding.

Olson *et al.* (*J. Virol. 73*(5):4145-4155 (1999); IDS Ref. AW5) generated a number of anti-CCR5 murine monoclonal antibodies (PA8, PA9, PA10, PA11, PA12 and PA14) from a screen of 10,000 hybridomas, of which six antibodies were able to inhibit HIV-1 envelope-mediated membrane fusion; all of these antibodies blocked fusion between CD4+ CCR5+ PM1 cells and HeLa- $Env_{JR\text{-}FL+}$ cells in a RET assay. However, of these antibodies, only PA14 blocked calcium mobilization induced by the chemokine RANTES, and the calcium mobilization inhibiting activity of monoclonal antibody 2D7 was superior to that of PA14 (Figs. 3A and 3B of

Olson *et al.*). Thus, as evidenced by Olson *et al.*, one of skill in the art did not have a reasonable expectation of success in producing an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor.

In view of the foregoing, it is clear that the requirements needed to establish the obviousness of the claimed invention in light of the cited references under *In re Vaeck* have not been met. For these reasons, Applicants respectfully submit that the combination of Chuntharapai *et al.*, Raport *et al.*, Samson *et al.* and Combadiere *et al.* do not render the subject invention obvious because the cited references, alone or in combination, do not teach or suggest all elements of the claimed invention and do not provide the ordinarily skilled artisan with a reasonable expectation of success in producing the claimed invention.

Furthermore, the Examiner's reliance on Wu *et al.* as evidence to support the obviousness rejection has apparently been based on improper hindsight reasoning, which is impermissible (M.P.E.P. § 2142, Original Eighth Ed., Latest Revision May 2004).

Thus, the combination of Chuntharapai *et al.*, in view of either Raport *et al.*, Samson *et al.*, or Combadiere *et al.*, as evidenced by Wu *et al.* does not render obvious Applicants' claimed invention. There is no teaching or suggestion to make an antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human CCR5, wherein said antibody or antigen binding fragment inhibits binding of MIP-1α, MIP-1β or RANTES, and inhibits one or more functions associated with binding of the chemokine to the receptor, nor is there any expectation of success in producing such an antibody or antigen binding fragment thereof. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 147-210 Under 35 U.S.C. § 103(a)

Claims 147-210 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chuntharapai *et al.* (U.S. Patent No. 5,543,503; IDS Ref. AD) in view of either Raport *et al.* (*J. Biol. Chem. 271*:17161-17166 (1996); IDS Ref. AW), Samson *et al.* (*Biochem. 35*:3362-3367 (1996); IDS Ref. AV), or Combadiere *et al.* (*J. Leukoc. Biol. 60*:147-152 (1996); IDS Ref. AT3),

as evidenced by Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4); and further in view of Ramakrishnan *et al.* (U.S. Patent No. 5,817,310).

Specifically, the Examiner states that Chuntharapai *et al.*:

> notes the suggestion of making antibodies specific for a chemokine family receptor such that the antibodies bind and inhibit receptor function. The human CCR5 receptor and chemokine ligands were known in the art as well as suitable assays for assessing binding and receptor function. The suggestion and means for screening are suitably provided and the making of such antibodies, while requiring extensive experimentation does not involve experimentation that is undue or not well established in the art. Thus, both suggestion and reasonable expectation of success are provided. Ramakrishnan further provides the suggestion and means for making suitable chimeric and humanized antibodies. (Office Action, page 24, first paragraph).

Applicants respectfully disagree. Chuntharapai *et al.*, Raport *et al.*, Samson *et al.*, Combadiere *et al.*, and Wu *et al.*, have been discussed *supra*.

Ramakrishnan *et al.* disclose immunoglobulins (antibodies) and fragments thereof that bind to PDGF beta receptor (see, for example, Abstract and columns 8-9). However, the disclosure of antibody fragments and chimeric antibodies which specifically bind to a *human PDGF beta receptor* does not render obvious an antibody fragment or chimeric antibody which specifically bind a different receptor, namely human CCR5, at the second extracellular loop and inhibit MIP-1α, MIP-1β, RANTES, or a combination thereof binding to that receptor, and inhibit one or more functions associated with binding of the chemokine to that receptor.

As discussed *supra*, Chuntharapai *et al.* with Raport *et al.*, Samson *et al.*, or Combadiere *et al.* and as evidenced by Wu *et al.*, do not teach or suggest all of the limitations of the instant claims, either alone or in combination. The teachings of Ramakrishnan *et al.*, fail to remedy these deficiencies. Thus, Ramakrishnan *et al.*, either alone or in combination with the other cited references, do not render the presently claimed invention obvious. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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